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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,934	TARARA ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-39,41,44,47-56,58,60,62-68,84-105,107 and 108* is/are pending in the application.

4a) Of the above claim(s) *23-37,84-102,107 and 108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41,44,47-56,58,60,62-68 and 103-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 12/10/08, in reply to the Office Action mailed 9/10/08, is acknowledged and has been entered. Claims 38, 54 and 104 have been amended. Claims 42, 57 and 106 have been cancelled. Claims 107 and 108 are newly added. Newly added claims 107 and 108, drawn to methods of making particulates are withdrawn at this time, as being directed to an invention that is independent or distinct from the invention originally elected for the following reasons: a pharmaceutical formulation for pulmonary administration could be prepared by another materially different method, such as by sonication, various coating methods, etc., as set forth in the Requirement for Restriction mailed 3/21/07. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 107 and 108 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 23-39, 41, 44, 47-56, 58, 60, 62-68, 84-105, 107 and 108 are pending, of which claims 23-37, 84-102, 107 and 108 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68 and 103-105 are readable upon the elected invention and are examined herein on the merits for patentability.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/08 has been entered.

Response to Arguments

Applicant's arguments with respect to the rejection of claims 38, 39, 41, 44, 47-56, 58, 60, 62-68, 103 and 104 under 35 U.S.C. 103(a) as being unpatentable over Weers *et al.* (WO 01/85136, whereby US 2002/0037316 is relied upon as equivalent) have been fully considered but are not persuasive, furthermore, they are moot in view of the new ground(s) of rejection due to changes in scope of the amended claims. The response to the applicant's argument is incorporated into the new grounds for rejection.

Double Patenting

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68 and 103-105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 11/187,757 for reasons set forth in the previous Office Action. Applicant's consideration of filing a terminal disclaimer in the Response filed 12/10/08 is noted.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 104 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a particulate pharmaceutical formulation in dry powder form for aerosolization and pulmonary administration which comprises an active agent particle having a geometric diameter of less than about 3 μm and at least one property of solubility in water of about 0.1 to about 1.0 mg/ml, or a low glass transition temperature, which comprises about 283 °C. The claim is confusing regarding the glass transition temperature. The recitation that the temperature "comprises about 283 °C" is ambiguous because it is unclear what temperatures are to be encompassed by the claim. The transitional term "comprising" is open-ended, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., >*Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). See MPEP 2111.03. Therefore, a temperature recited as "comprising about 283 °C" may be interpreted to read 283 plus any other value, therefore the temperature is not clearly defined. Tg is typically a specific value and the recitation "comprises about" may encompass multiple unlimited temperatures. As such, the metes and bounds of

the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38, 39, 41, 44, 47-56, 58, 60, 62-68 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weers *et al.* (WO 01/85136, whereby US 2002/0037316 is relied upon as equivalent), as evidenced by Weickert *et al.* (US 2002/0177562), Wiedmann *et al.* (*J. Controlled Release*, 2000, 65(1-2), p. 43-7), and Didriksen (WO 00/01365).

Weers discloses dry powder compositions of phospholipids which are efficiently delivered to the deep lung. The phospholipids may be administered alone or in combination with an active agent. The composition may be administered via a simple

passive DPI device (paragraph 0011). The active agent may be ciprofloxacin (which inherently has the claimed solubility), amphotericin (i.e. which inherently has the claimed solubility), flunisolide (which inherently has the claimed solubility), etc. (paragraph 0022). Weers clearly teaches both soluble and insoluble actives (and dispersions thereof) in feedstock preparation. See paragraph 0022. See also paragraph 0062, wherein the active agent may also be dispersed directly in the emulsion, particularly in the case of water insoluble agents. Both water-insoluble (e.g. budenoside) and water soluble (e.g. nicotine bitratrate) drugs are exemplified (see Examples V or IX).

The medicament possess special physicochemical properties, such as high crystallinity (paragraph 0060), and include hollow porous aerodynamically light microparticles with particle diameters appropriate for aerosol deposition into the lung (paragraph 0065 and 0048).

The medicament is formulated in a way such that it readily disperses into discrete particles with an **MMD** which is preferably from **0.5 – 5 μm** (i.e. less than 10 μm, as claimed); a **MMAD** preferably from **1** – 4 μm (i.e. including less than about 2.6 μm, as claimed) (paragraph 0043). The powders typically have a **bulk density** less than 0.1 g/cm^3, or preferably less than **0.05 g/cm^3**, as claimed (paragraph 0049). The **geometric diameter** is preferably less than **2.5 μm** (i.e. which is less than 3 μm, as claimed) (paragraph 0070).

Phospholipids from both natural and synthetic sources are compatible with the present invention and may be used in varying concentrations to form the structural

matrix. Exemplary phospholipids useful in the disclosed stabilized preparations include dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, etc. (paragraph 0032). Regarding claims 49-51, the particulate compositions may be used in conjunction with metered does inhalers, dry powder inhalers or nebulizers for liquid dose instillation techniques (paragraph 0042). Regarding claim 52, the powders can include a polyvalent cation (abstract). Regarding claim 53, the particles are made by spray-drying with a blowing agent (paragraph 0058). Regarding claim 41, it is noted that Weers does not specifically recite a fine particle fraction of his formulation. However, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. It is interpreted, absent evidence to the contrary, that since Weers discloses particles of the same active agents (i.e. thus having the same solubility), and teaches that the particles are the same sizes (i.e. MMD, MMAD and geometric diameters) less than those is claimed, same bulk density, etc., and are made by the same methods as those claimed, the particles would inherently be capable of having the claimed inherent features such as fine particle fraction.

Regarding claim 104, with respect to the limitation that the active agent particles have a low Tg, comprising about 283 C, it is interpreted, absent evidence to the contrary, that the formulations of Weers would inherently meet this limitation because Weers teaches the same actives as those which are now claimed (e.g. amphotericin). Thus, the same active agent particles would inherently have the same Tg as that which

is now claimed. This interpretation is supported by Applicants own specification, which recites that active agents have an inherent Tg (see published paragraph 0007 of specification). With regard to the limitation that the formulation is prepared by preparing a suspension of active agent particle and phospholipid and spray-drying, Weers also meets this limitation. See paragraph 0064, whereby the active agent may be solubilized (or dispersed) directly in the emulsion. In such cases, the active emulsion is simply spray dried without combining a separate active agent preparation. Furthermore, such a limitation appears to be a product-by-process type limitation. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

The instant claims require that the particulates do not comprise lactose. While it is noted that Example V demonstrates lactose, Weers clearly teaches that conventional DPIs comprise powdered formulations and devices where a predetermined dose of medicament, either **alone** or in a blend with lactose carrier particles, is delivered as an aerosol of dry powder for inhalation (paragraph 0042). Weers further teaches that by providing particles with very low bulk density, the minimum powder mass that can be filled into a unit dose container is reduced, which **eliminates the need for carrier**

particles. That is, the relatively low density of the powders provides for the reproducible administration of relatively low dose pharmaceutical compounds. Moreover, the elimination of carrier particles will potentially minimize throat deposition and any "gag" effect, since the large lactose particles will impact the throat and upper airways due to their size (paragraph 0049).

Weers does not specifically recite the solubility of various active agents which may be used in the invention. It is for this reason that Weickert, Wiedmann and Didriksen are joined.

Weickert discloses that the aqueous solubility of amphotericin is 0.2 mg/ml (see Table 1).

Wiedmann discloses that the aqueous solubility of flunisolide is 1.2 μg/ml (i.e. 0.12 mg/ml) (see Abstract).

Didriksen discloses that ciprofloxacin has a solubility in water ranging from 0.1-0.3 mg/ml (see Abstract and page 8, lines 4-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a pharmaceutical formulation for pulmonary administration comprising porous particulates of amphotericin, ciprofloxacin, flunisolide, etc. in a matrix comprising a phospholipid having the claimed water solubility, geometric diameter, mass median diameter, bulk density, and mass median aerodynamic diameter, wherein the particulates do not comprise lactose. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Weers teaches that such active agents may be incorporated into such formulations with

phospholipid for pulmonary administration (paragraph 0022). While Weers does not specifically recite the solubility of said active agents, Weers teaches that water soluble or water-insoluble agents may be incorporated into the formulations. Such active agents inherently have the claimed solubility, as evidenced by Weickert, Wiedmann or Didriksen. Regarding the presence of lactose in the formulation, Weers teaches that the relatively low density of the powders provides for the reproducible administration of relatively low dose pharmaceutical compounds. Moreover, the elimination of carrier particles will potentially minimize throat deposition and any "gag" effect, since the large lactose particles will impact the throat and upper airways due to their size (paragraph 0049), therefore one would have been motivated to eliminate lactose from the formulations since Weers teaches that elimination of lactose carrier particles.

Applicant argues on pages 11-12 of the Response that Weers does not teach, suggest or disclose an active agent having a low solubility specifically defined as being between about 0.1 to about 1.0 mg/mL, nor does Weers teach a particulate engineered for pulmonary administration wherein the particulate composition comprises an insoluble particle having a geometric diameter of less than about 3 microns dispersed within a phospholipid matrix.

This is not found to be persuasive. Weers teaches that soluble or insoluble active agents may be employed (see paragraph 0022 or 0062). With regard to active agents having a solubility from 0.1 to 1.0 mg/mL, Weers teaches at least amphotericin, ciprofloxacin, flunisolide, which inherently have the claimed solubility, as set forth

above. The Weers document need not recite the solubility (or other physical properties) of each and every drug which is suitable for his application. With regard to geometric diameter, Weers teaches that the geometric diameter is preferably less than 2.5 μm (paragraph 0070).

Applicant further argues on page 12 of the Response that as Applied to claim 104, Weers does not teach a particulate engineered for pulmonary delivery comprising active agent particles having a geometric diameter of less than 3 micron and at least one property of a solubility in water of about 0.1 to about 1.0 mg/ml, or a low glass transition temperature which comprises about 283 C, and a porous phospholipid matrix material. Applicant contends that the Examiner's assertion that Weers teaches an active having a low Tg is inaccurate, particularly with respect to the position that amphotericin has a low Tg. Applicant asserts that Weers does not address this parameter at all, and further states that it cannot be predicted positively that a particular Tg is inherent in a material. Applicant further argues that the claim is not limited to amphotericin, thus the Tg recited therein cannot be said to be an inherent property of the claimed material.

This is not found to be persuasive. Applicant's own specification recites that active agents have an inherent Tg (see published paragraph 0007 of specification). Weers teaches the same actives as those which are now claimed (e.g. amphotericin),thus, it is interpreted absent evidence to the contrary, that the same active agent particles would inherently have the same Tg as that which is now claimed. See MPEP 2112. The express, implicit, and inherent disclosures of a prior art reference

may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). The Weers need not recite every physical property of active agents (e.g. Tg) which are suitable for his application.

Applicant argues on pages 12-13 of the Response that the claims have been amended to specifically exclude lactose, citing Example 5 of Weers which incorporates an excipient.

This is not found to be persuasive. Weers teaches that conventional DPIs comprise powdered formulations and devices where a predetermined dose of medicament, either alone or in a blend with lactose carrier particles, is delivered as an aerosol of dry powder for inhalation (paragraph 0042). Weers further teaches that by providing particles with very low bulk density, the minimum powder mass that can be filled into a unit dose container is reduced, which eliminates the need for carrier particles (paragraph 0049), as set forth above. A reference is not limited to what is taught by the Examples.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS